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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/884,873 06/30/97 COOK P ISIS-2202

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EXAMINER

GARCIA, M

ART UNIT

PAPER NUMBER

1627

20

DATE MAILED: 05/21/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary

Application No.

08/884,873

Applicant(s)

Cook

Examiner

Maurie E. Garcia, Ph. D.

Art Unit

1627

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE THREE MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Mar 2, 2001

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 35 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 2-5, 7-12, and 33 is/are pending in the application

4a) Of the above, claim(s) _____ is/are withdrawn from consideration

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 2-5, 7-12, and 33 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirements

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

19) ☐ Notice of Informal Patent Application (PTO-152)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

20) ☐ Other: _____

DETAILED ACTION

1. The Response filed March 2, 2001 (Paper No. 19) is acknowledged. Claims 6, 13, 24-30 and 34-36 were cancelled, claims 5 and 33 were amended and no claims were added. Therefore, claims 2-5, 7-12 and 33 are pending.

Withdrawn Rejections

2. The previous rejections under 35 USC 112, first and second paragraph, are withdrawn in view of applicant's cancellation of claims and claim amendments.

New Rejections – Necessitated by amendment Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 2-5, 7-12 and 33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The specification as originally filed does not provide support for the invention as now claimed. The claims are directed to a mixture, not a single compound. It is not apparent that applicant had support for mixtures wherein T is *not* a single bond. The removal of T as a selection in the Markush group is new matter because there is not support for such “sub-generic” mixtures. Applicant points to libraries 59-62 and examples 109-113 for support for this new claim; however, while these examples show selections for T that are not single bonds, it is not clear support for the removal from the claim of such a limitation. There are several examples in the specification that *do* depict T as a single bond and applicant does not appear to be in possession of the “sub-generic” libraries that specifically limit T to other than a bond. In accordance with MPEP § 714.02, applicants **should specifically point out support** for any amendments made to the disclosure. Also, in order for a negative limitation to be added to a claim, that particular limitation must be *specifically* recited in the specification.

Maintained Rejections
Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

6. Claims 2-5, 7-12 and 33 remain rejected under 35 U.S.C. 102(a) as being anticipated by Gordeev et al (WO 96/33972).

Gordeev et al disclose methods for synthesizing libraries of pyrimidine compounds (see Abstract). The library compounds of Gordeev et al have the claimed heterocyclic scaffold and substitution pattern (see page 34-35 and more specifically page 81) and are substantially homogeneous (page 35, bottom). The library compounds are made in a pooled format (see page 84, lines 18-28), for example, a pool of 21 pyrimidines is made and tested. This reads directly on the limitation of a mixture of at least 6 compounds and the further limitations of claims 2 and 3. All compounds are present in at least some of the pools and the compounds are synthesized at a purity (see page 81) where the mixture would be close to equimolarity. The pyrimidine compounds of Gordeev et al have at least three functionalizable atoms, at least one of which is nitrogen (see pages 81-85). In the compounds of Gordeev et al the tethers can be considered to be bonds for two of the side groups and the amine moiety could be considered a tether moiety (NHR¹). This meets the limitations of claims 5 and 7-10. The building blocks of the library comprise various leaving groups (see page 83), reading on the limitations of claims 11 and 12.

Response to Arguments

7. Applicant's arguments filed March 2, 2001 have been fully considered but are not found persuasive. The examiner's rationale is set forth below.

8. First applicant argues that Gordeev teaches compounds that are substituted at the 5 position on the pyrimidine ring. While the reference does show some compounds with this substitution, the library specifically referred to by the examiner (specifically page 81 of the reference) show the same 2, 4, 6 substitution on the pyrimidine ring as the claimed compounds.

9. Applicant argues the claims as amended, that is, with the removal of the selection of T being a single bond. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., T is not a single bond) were *not* recited in the previously rejected claim(s). Applicant states that Gordeev teaches functional groups attached to the pyrimidine ring without tether moieties (i.e. T = single bond). The examiner agrees that the R₃ and R₄ moieties in the library of Gordeev depicted on page 81 of the reference are attached to the ring via bonds. However, the reference does disclose that the third substituent is attached through an amine moiety which reads on the instant tether moiety (NHR¹).

10. Since the examiner deems applicant's removal of the selection of T being a single bond from the Markush group in the instant claims to be new matter (see above), the rejection of the claims as being anticipated by Gordeev et al is maintained.

Maintained Rejections
Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

12. Claims 2-5, 7-12 and 33 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Grandoni (US 5,998,420) in view of Hamprech et al (US 5,591,694) in view of Gordon et al (Of record, J. Med. Chem. 1994, Vol. 37, No. 10, pp. 1385-1401).

Grandoni et al teach sulfonylurea herbicides that read on the claimed compounds (see Figures 3 & 5, for example). The pyrimidine compounds have least three functionalizable atoms, at least one of which is nitrogen, oxygen and/or sulfur and have groups that can be considered tethers (see structures S, T, U and V in Figure 5 and compound at the bottom of Figure 6). The building blocks of the library comprise various leaving groups (see column 9, top). In the context of creating better inhibitors of acetolactate synthase (beginning in column 8 and going through the top of column 10), Grandoni et al teach the concept of “combinatorial optimization of inhibitory sulfonylureas” (column 9). The activity of such compounds reads on the limitations of claims 24-26.

Hamprech et al also teach sulfonylurea herbicides (see Abstract). These compounds also read on those in the claimed mixture and have similar substitution to those of Grandoni. Hamprech et al teach that compounds with

improved properties are needed and that to do so, varying the substituents on the pyrimidine moiety is a preferred method of doing so (see column 2, lines 12-23).

Grandoni and Hamprech et al lack the teaching of creating a mixture of at least 6 compounds.

However, Gordon et al teaches that “[w]hen small molecule leads for a target have been previously defined...the notion of searching for more potent derivatives among libraries combinatorially enriched in specific pharmacophore analogs is an obvious tactic to pursue” (p.1386 Column 1, 1st full paragraph). Also, Gordon et al teaches the general principles of combinatorial chemistry and the rationale for creating libraries, see page 1385 and 1397-1401 generally. Specifically, the notion of intentional biasing as a form of drug design is taught (see page 1401, 1st column). Gordon et al teaches a “spectrum of molecular diversity” (see page 1397, Figure 19) that describes why a library of a certain size would be useful for a variety of different applications.

Therefore, it would have been *prima facie* obvious to one of ordinary skill to create a mixture (i.e. library) of six or more compounds of the claimed type based on the teachings Grandoni and Hamprech et al as to the synthesis and uses of such compounds and the teachings of Gordon et al regarding libraries. A person of ordinary skill in the art would have been motivated to create libraries to have large numbers of molecules available for testing for improved properties (see Gordon, page 1398, 1st paragraph).

Response to Arguments

13. Applicant's arguments filed March 2, 2001 have been fully considered but are not found persuasive. The examiner's rationale is set forth below.

14. Again, applicant argues the claims as amended, that is, with the removal of the selection of T being a single bond. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., T is not a single bond) were *not* recited in the previously rejected claim(s).

15. With respect to the rejection under 103, however, not only is the rejection maintained because the examiner deems applicant's removal of the selection of T being a single bond from the Markush group in the instant claims to be new matter (see paragraph 10 above), but the references cited in the rejection also teach compounds where each substituent is attached to the pyrimidine ring through a tether moiety that is not a bond.

16. Applicant states that "[n]o selection of tether T and letter L of the claimed compounds...will give the thiourea compounds reported in Grandoni and Hamprechet" (Response, page 6). The examiner respectfully disagrees. Grandoni teaches a compound labeled "8 KIH-2031/DPX-PE 350" on the bottom of Figure 6 that reads on the claimed compounds of structure I when T is O in two instances and S in the other instance; two of

the L moieties are alkyl (CH₃) and the last L moiety is a substituted carbocyclic moiety. Hamprechet also teaches compounds with the same 2, 4, 6 substitution on the pyrimidine ring (R⁸ in the patent is H or halogen and when it is H reads on the claimed compounds). The substituents are attached to the ring via an N, O or S atom, reading on the claimed T moieties. The substituent moieties of Hamprechet read on the claimed L groups of alkyl, alkenyl or alkynyl (or substituted versions thereof); see structure IIIa of the patent in column 2.

17. Applicants also argue that the “combination of references does not produce the claimed invention” (Response, page 6). In response to this argument, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). As stated above, Gordon teaches that “[w]hen small molecule leads for a target have been previously defined...the notion of searching for more potent derivatives among libraries combinatorially enriched in specific pharmacophore analogs is an obvious tactic to pursue”.

18. In this case, the examiner maintains that the *combined* teachings of the cited references render the claimed invention obvious. The teachings referred to above

(paragraph 17) are strong motivation. Also, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). In the instant case, the beneficial result of the combination of references is creating a library of compounds having a known utility from which to screen for more active members. Such benefits of combinatorial optimization were well known in the art, as taught by Gordon. Specifically in reference to compounds having the "core structure" of the claimed mixtures, see Grandoni regarding the concept of "combinatorial optimization of inhibitory sulfonylureas" (column 9).

Status of Claims/Conclusion

19. No claims are allowed.

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

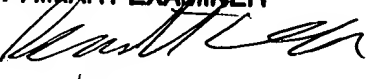
A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the

advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maurie E. Garcia, Ph.D. whose telephone number is (703) 308-0065. The examiner can normally be reached on Monday-Thursday from 9:30 to 7:00 and alternate Fridays.

22. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat, can be reached on (703) 308-2439. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BENNETT CELSA
PRIMARY EXAMINER


Acting SPE

Maurie E. Garcia, Ph.D.
May 18, 2001